EXHIBIT B

Translation of Opposition of Fuchs, Luderschmidt & Partner, Patent Attorneys, filed in the German Patent Office in Munich on 6 February 1997

German Patent 44 47 287
Patentee: Cevc, Gregor, Prof. Dr., 85551 Kirchheim, Germany
Opponent: ROVI GmbH

In the name of ROVI GmbH, Breitwiesenstrasse 1, 36381 Schlüchtern, an

OPPOSITION

is lodged against German Patent 44 47 287 of Prof. Dr. Gregor Cevc, 85551 Kirchheim, the title of which is "Prepärat zum Wirkstofftransport durch Barrieren" (Preparation for the Transport of an Active Agent through Barriers). The Opposition is based on the grounds of opposition according to § 21, Section 1, Nos. 1, and 2, German Patent Law.

It is requested

- to revoke the patent in its entirety,
- as an auxiliary, to fix a date for Oral Proceedings, and
- to give the Opponent sufficient time for a response to the of the counterstatement Patentee.

An authorization will be filed later.

Reasons

I.

The attacked patent comprises two independent claims, namely a product claim 1 and a method claim 22.

In claim 1, a preparation is claimed, which is in the form of droplets, suspended in a liquid medium for the transport of an active agent through barriers and constrictions, wherein the preparation is characterized by the following features:

A. The fluid droplet comprises a membrane-like sleeve, being comprised of one or more layers of amphiphilic carrier substances, wherein

B. the carrier substance comprises at least two (physico) chemical different components;

(generic part)

C. the at least two components show different solubility by a factor of at least 10in the suspension medium of the preparations, and

E) a) either the content of solubilizing components is less than 0.1 mol %, referring to the total amount of these substances, at which the point of solubilization of the covered droplets is reached, or

b) the point of solubilization cannot be reached.

(characterizing part)

In claim 22 a method for manufacturing a preparation having the above features A and B is claimed. The characterizing features of this method are:

E. Selection of at least two amphiphilic components, having a solubility in the suspension medium of the preparation which differs by a factor of at least 10, wherein

F. a) either the amount of solubilizing substances is less than 0.1 mol %, referring to the total amount of these substances, at which the point of solubilization of the covered droplets is reached, or

b) this point cannot be reached in the range of practical relevance; and

G. the amount of amphiphilic components is adjusted in such a way that the ability of the preparation to permeate through constrictions is at least 0.01 thousandth of the permeability of small molecules.

(characterizing part)

II.

The following prior art documents are cited:

D1 EP 0 475 160 (mentioned in the attacked patent on page 3, line 21)

D2 A. Helenius and K. Simons, "Solubilization of membranes by detergents", from Biochemica et Biophysica acta 415 (1975), pp. 29-79

D3 A. Schreier, "Liposomen- ein neuartiger Arzneistoffträger" (Liposomes – a novel drug carrier), Pharmazie in unser Zeit, 1982, pp. 97-108

D4 L.F. Fieser, M. Fieser, Organische Chemie (Organic Chemistry), 1968, page 1250

D5 J.M. Clark, Experimental Biochemistry, 1964, pp. 47-48.

Without any doubt, the closest prior art is D1. In this document (having the same inventor as the attacked patent) transfersomes are described, which comprise, besides an amphiphilic

substance, a surface-active substance, in an amount of 0.1 – 99 mol% of the amount, at which the point of solubilization of the transfersome droplets is reached, besides an amphiphilic substance. This amount of surface active substance should (allegedly) result in an optimised approach to the limit of solubilization of the transfesomes, so that these are sufficiently elastic, in order to get through the constrictions in a barrier, for example in the skin (see attacked patent, page 3, lines 20-28).

Setting out from this prior art, the inventors of the attacked patent thus formulated the following objects:

1. Not to be restricted by the ranges mentioned when formulating such highly permeable preparations.

2. To name transfersomes, which either do not have a point of solubilization, or are far away from the point of solubilization, for the application of active agents, which allow their faster and more effective transport through barriers and constrictions.

3. To provide transfersomes for the transport of active agents through human, animal and vegetable barriers, which allow an improved availability of the active agent at the place of effect.

4. To provide a method for the manufacture of such transfersomes for the transport of active agents.

Objects 1-3 should be solved by the characterizing features C and D of claim 1, wherein the features A and B, which form the generic parts of claims 1 and 22, have been taken from D1, and object 4 should be solved accordingly by features E-G of the method claim 22.

Feature C is not disclosed in D1, literally. However, when taking into consideration the possibilities of combination of a lipid (amphiphilic substance) and a surface-active substance, which can be derived from the individual lipids described on pages 4 and 5, and the possible surface-active substances described on pages 6-13 (!) which may be derived from claim 1 of D1, one has to recognize that with any random selection of two components, a difference in solubility of only a factor of 10 is more likely the rule than the exception.

In any case, feature C of claim 1 is *de facto* also disclosed in D1.

Feature D is composed of two alternatives. The alternative D.a) is novel in view of D1, but forms a complete continuation of the lower limit of the 99 – 0.1 mol % mentioned in D1.

Feature D.b) is different. This alternative is supported in the description by two different statements:

1.) On page 3, lines 50/51:"... or the amphiphilic components are selected in such a way that independent of the concentration, no solubilization of the covered droplets occurs at all".

    This unambiguously means that a carrier formed from two amphiphilic components A and B is not solubilized at any given ratio of mixture A:B.

2.) On page 4, lines 67 and 68: "...or this solubilization is in fact not achievable in the range of concentrations which are practically relevant."

Since the above variant 1) is included in claim 2, which is dependent from claim 1, the alternative D.b) consequently must comprise both variants. However, this is only possible with the meaning that not achieving the point of solubilization is possible, either by adjusting

the ratio of components A:B, as well as by the properties of the components (according to claim 2). The first means that both components A and B may be present in a ratio A:B, at which a solubilization is achieved, but the actual ratio A:B at the relevant range of concentration does not make a solubilization possible, i.e. the concentration of the solubilizing compound component B is far off from its corresponding concentration, at which solubilization would occur.

However, since the alternative D.b) is an alternative to D.a), this means that the concentration of the soulubilizing component must be more than 0.1 mol %, referring to the amount of this substance, at which solubilization occurs.

Such carriers, however, having a "relevant" ratio of components, where the point of solubilization cannot be achieved, are described in D1 (component B > 0.1 to 99 %).

Consequently, all features of claim 1 including the alternative D.b) are anticipated by D1.

However, this is not true for the above variant of features, where the amphiphilic components are selected in such a way that, independently of concentration, no solubilization at all of the covered droplets occurs. This feature, preferably selected in claim 2, strangely enough does not occur in the method claims.

III.

For evaluating inventive activity, one has to look at the object(s) in relation to the solution, at best.

As already pointed out above, the condition according to feature C or E, respectively, is in view of the possibilities of combinations in D1, met more as a rule that as an exception. Such compositions are given, for example, also in D2, in the ternary phase diagram of Fig. 5 on page 42.

Conditions which are nearly unavoidable in view of the prior art, cannot establish inventive activity, even not if they are given in parameters.

Feature Da) is not included in the prior art, and not suggested. However, the importance of this alternative is not derivable from the attacked patent. In none of the examples given, was the point of solubilization for a given mixture of components determined and then correspondingly, the solubilizing component adjusted specifically to a value below 0.1 % of the solubilizing concentration.

Furthermore, an amount of < 0.1% without any further information about a lower limit means that, for example, phosphatidylcholin "contaminated" with trace amounts of fatty acids may fulfil feature Da) (see D2, Table I, on page 31). One can understand from D4, page 1250, which acids are present in the soja-lecithin, which is used throughout the mentioned patent. From D5, pages 47-48 (especially points 3 and 6), one can learn about the difficulties of isolating lipids from living tissue, so that one can set out from the fact that dependent from the quality of isolation, fatty acids and their salts are present in preparations made of phosphat idylcholin from soja above 0.1 % of the point of solubilization, as well as below 0.1 % , without being added separately.

This would then also lead into the scope of the alternative Db).

The only features not appearing themselves in the prior art, is the variant mentioned in claim 2, which may be subsumed under Db), the selection mentioned in claim 2 would be selected

specifically and would not be the product of pure chance, resulting from a combination of components having no possibility of solubilization. When only having a look at the preparation, one cannot see at all if the components have been selected specifically, or if they do not have a point of solubilization by pure chance.

Interestingly, this feature based on a method step ("selection") does not appear in the real method claims 22-33 at all! On the contrary, in the according alternative Fb of the feature of method claim 22, the addition "in the practically relevant range" may be found, which excludes a method-like measure, according to claim 2 (specific selection). There is no practical relevant range with two components which do not show solubilization in any ratio of mixture.

This makes clear that the feature variant according to claim 2 is a verbal delimitation against D1 only, which does not contribute anything to inventive activity. The only feature which extends beyond the disclosure of D1 is the feature G, including the corresponding dependent claims 23 and 24.

IV.

In feature G of method claim 22, the adjusting of the amount of amphiphilic components is limited by the permeability of the carriers which should be at least the $100{,}000^{th}$ part of the permeability of small molecules, for example water.

This single feature extending beyond the disclosure of D1 is, however, in no way suited to characterize the carriers of the attacked patent, or to delimit them, respectively.

In particular, the central term "permeability" is not disclosed completely enough to be carried out by a person skilled in the art. What the description says about permeability triggers many more questions than are answered.

This problem becomes clear if one tries, as a person skilled in the art, to fulfil the above-mentioned objects 3 and 4, for example the preparation of transfersomes for the transport of an active agent through skin (see, in particular the generic terms of independent claims 1 and 22).

In order to be able to decide if one is within or without the scope of the attacked patent, one has to determine the permeability of used vesicles, in any case, and to relate these values to the permeabilities determined for small molecules, for example water (see also description, page 8, lines 6-26).

The definition of the term "permeability" or ability of permeation (P), respectively, is given on page 10. There, one can learn that P is the amount of penetrate, which is driven through an artificial permeation area per unit of time, per unit of area, and per driving force.

Some essential questions are left unexplained here:

1. What is the amount of permeate?

   According to feature G of claim 22, the permeation capability of the preparation through constrictions has to be determined. According to the generic term of the claim, the preparation is in the form of a fluid droplet suspendable (not suspended!) in a liquid medium, that is the preparation is made of carrier vesicles.

According to the description on page 10, the permeation capability of the carrier suspension (line 43) is determined instead, i.e. the amount of permeate (amount of material) is made of the preparation + suspension medium.

The suspension medium itself is made of such small molecules which according to feature G have a permeability of 100,000-times the permeability of the preparation, i.e. the carrier, as a rule!

2. Are equal numerical values obtained for P, independently of the method of determination of the penetrated amount of the material (volumetrically or gravimetrically, page 10, line 42)? This may only be the case, if the specific weights of the determined carrier suspension (lipid vesicles + suspension medium) is equal to 1.

   If this is not the case, it might be that one would lie in one case within the scope of the patent, and in the other case out of the scope, for the same carrier suspension.

3. Are the time, the area and the driving pressure the only parameters, on which the amount of penetrate is dependent?

   Hardly not. What affects do the temperature, the viscosity (see page 10, line 30) and the ratio of the pore diameter of the restriction (membrane) in relation to the vesicle size (page 7, line 52) have on the permeability?

   For a specific object (vesicle for the transport through the skin) one would at first have to determine the permeability of water. But at which temperature? Water shows different densities and viscosities at different temperatures.

a) In view of the object, it has to be suggested to choose a temperature of 37°C (body temperature). Within the examples of the attacked patent, two different (and further, non-physiological) temperatures are given (Examples 1-4 each 62°C, (page 10, line 54) and Example 7, 52°C).

One must be taken aback if one reads whereupon the selection of these temperatures depends. The 62°C temperature was chosen to secure that both lipids are present in a fluid phase (page 10, lines 54-55).

A fluid phase is unambiguously either a liquid or a gas. Are the lipids in a liquidized form capable of functioning as active agent carriers?

b) That the vesicle bursts thereupon, follows from Table 1, page 11, where the carriers are much smaller after the permeation than before, which means that they must have been re-formed during the penetration, namely in approximately the size which corresponds to the pore diameter (if one assumes that the pore diameter of the barrier in Examples 1-4 is the same as in the Examples 5-6).

Such processes however are also used in the prior art in order to condition carriers of usual liposomes to a predetermined size, for example by pressure-filtration through polycarbonate membranes (see D3, page 100, left column, first paragraph) (see also method claim 31).

Now, one has to ask the question if such a behaviour may be subsumed under the term stability or deformability (or elasticity) according to the description of the attacked patent, see for example, page 3, lines 27 and 57; page 4, line 65; page 7, line 50; page 8, line 7. In particular, on page 13, line 17, it is stated that the carrier permeation capability is a measure for the carrier deformability. Having a look at

the term "deformability" in the context of the term "stability" (for example, on page 4, line 18; on page 8, line 8, and on page 10, line 6), one should, in our opinion, expect that this deformability occurs only temporarily, when permeating through the constrictions of the barrier, whereupon the higher permeation capability against simple liposomes should be based.

At which temperature should now the permeability of the suspension be measured in the actual problem (transport of active agents through skin?) The carriers according to the Examples 1-7 of the attacked patent are obviously not suitable for this purpose.

c) Even the viscosity, which is dependent from the number and size of the carriers suspended in the suspension medium should play a major role in the determination of the material amount penetrating per unit of time. At which viscosity have the permeabilities of the examples of the attacked patent been determined? Depending on the viscosity of the suspension, one would then in the extreme case, have the same situation that with the same carrier (only the carrier or its preparation is claimed) in one case one would fall into the scope and in the other case, out of the scope of the patent.

Which gradient should or could be used for driving the suspension through the barrier (page 7, lines 30-33)? Does it make any sense to use pressures in the range of megapascals for active substance carriers through skin, which are light-years away from physiological conditions?

How was the permeation capability of the Examples of 1-4 and 5-6 determined? According to Table 1 on page 11, the permeation capability is given for defined

carrier compositions at 5 different pressures (between 0.3 and 0.7 MPa), as well as in Table 2 for 100 nm pore diameter.

For example, in Table 1, a numerical value of 10.9 of the permeation capability was given for the above charge at a pressure of 0.5 MPa. It is only clear that the permeate has been determined volumetrically.

According to the column's heading, this value should be 10.9 µl per 1 MPa, 1 sec and 1cm². However, this cannot be true, since according to column 1, it was measured at a pressure of 0.5 MPa.

An extrapolation of the value actually determined at 0.5 MPa to 1 MPa is also not possible, since this value is far exceeded already at a pressure of 0.6 MPa. Furthermore, there should be a distinctly non-linear relationship between permeation capability and driving force (page 10, lines 56-60) as a criterion for distinction between transfersomes and liposomes.

This makes clear that for the permeation capabilities, more factors play a major role than disclosed in the attacked patent, so that the disclosure of the attacked patent is not sufficient to enable the person skilled in the art to reliably or reproducibly carry out the measure disclosed in feature G of method claim 22.

Thus, the attacked patent is also to be revoked for the grounds of § 1, Sec. 1, No. 2 of the German Patent Law.

To summarize, the initial request for revocation of the attacked patent in its entirety is fully justified.

Signed by Dr. Luderschmidt, Patent Attorney

Encl.:

D1-D5